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Remarks/Arguments

Claims 1-59 were pending before this response. Claims 13-36 and 42-59 have been withdrawn from consideration as being directed to a non-elected invention, and claim 3 has been cancelled. Claims 1 and 37 have been amended as set forth in the above "Listing of the Claims." As amended, the claims are supported by the specification and the original claims. In particular, the amendments to claim 37 are supported, for example, at page 62, lines 25-31. Thus, upon entry of the amendments, claims 1, 2, 4-12 and 37-41 will be pending.

Objections to the Specification and Claims

The specification of the present application was objected to due to the following informalities, as set forth on pages 2-3 of the Office Action. It is respectfully submitted that the amendments to the specification, as set forth above, remedy these informalities. Withdrawal of the objection is respectfully requested.

The specification is objected to as allegedly not conforming to 37 C.F.R. 1.821(d) due to the absence of the appropriate sequence number regarding amino acid sequences at pages 12, 66, and 76. It is respectfully submitted that the amendments set forth above remedy the absence of the appropriate numbers and direct insertion of the corresponding Sequence Listing into the specification. The sequence listing in computer readable format as well as the appropriate statement as required by 37 C.F.R. § 1.822 to 1.824 are attached herewith. Accordingly, withdrawal of the objection is respectfully requested.

The specification is objected to as allegedly containing an embedded hyperlink and/or other form of browser-executable code on page 27. It is respectfully submitted that the embedded hyperlink has been deleted. Accordingly, withdrawal of the objection is respectfully requested.

The specification is objected to as allegedly lacking proper notation to a Figure reference on page 97. It is respectfully submitted that the amendments set forth above remedy the absence of the Figure number. Accordingly, withdrawal of the objection is respectfully requested.

The specification is objected to as allegedly failing to indicate the extent of public availability regarding Gen Bank Accession No. AF105220 on pages 6, 12, 24, and 66. It is respectfully submitted that the amendments set forth above clarify the extent of public availability of Applicant's deposit statement. Accordingly, withdrawal of the objection is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph

Applicant respectfully traverses the rejection of claims 37-41 under 35 U.S.C. § 112, first paragraph, for containing subject matter allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the invention at the time of filing of the Application. In particular, it is alleged in the Office Action at page 5 that the specification fails to teach how to use a JSRV or JSRV polypeptide to induce an immune response having a pharmaceutical effect in a subject. The Examiner asserts that it is the position of the Office that the meaning of a pharmaceutical composition is that the composition must have a therapeutic benefit, and that solely inducing an immune response is not a therapeutic benefit.

A therapeutic benefit, by definition, is anything that promotes healing or provides medical treatment (Webster's II New College Dictionary, Houghton Mifflin Co., 1995). Applicant submits that the specification provides an enabling description of a therapeutic benefit to inducing an immune response in a subject at page 62, lines 25-31, which teaches that "Env protein(s) are particularly useful in sensitizing the immune system of an animal such that, as one result, an immune response is produced which ameliorates the effect of an infection by a JSRV

or related viral particle." Exhibit A is a copy of the relevant sections of a textbook disclosing that sheep naturally infected with JSRV, and developing the associated lung cancer do not develop antibodies to the virus. Thus in the natural setting, the JSRV disease occurs in the absence of a humoral immune response. However, Applicants have found that animals inoculated with recombinantly expressed JSRV CA (gag) or SU (envelope) proteins do raise antibodies. (*Current Topics in Microbiology & Immunology,* Vol. 275, page 69). Thus, when a subject is suffering from the effects of natural infection by JSRV, inducing an immune response provides the therapeutic benefit of alleviating the symptoms associated with infection. Applicant has amended claim 37 to include the limitation "wherein the immune response ameliorates the effect of an infection by a JSRV or related viral particle." Accordingly, Applicant submits that amended claim 37, and dependent claims 38-41 are sufficiently described by the specification to meet the requirements of 35 U.S.C. § 112, first paragraph and respectfully requests withdrawal of the rejection under § 112, first paragraph.

The Examiner further rejected claims 37-41 as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. More specifically, the Examiner alleges at page 4 of the Office Action that the nature of the invention is the administration of a retrovirus or retroviral polypeptide to a subject in order to induce an immune response against the virus or polypeptide that will achieve a therapeutic benefit, and that the state of the art regarding Jaagsiekte sheep retrovirus (JSRV) is that there are no treatments or vaccines. Further, the Examiner claims that the breadth of the claims is unreasonable and that the specification fails to provide guidance or working examples to show how to achieve a pharmaceutical benefit using a JSRV or JSRV peptide. Finally, the Examiner concludes by alleging that the quantity of experimentation needed to make or use the invention based on the content of the disclosure is undue. Applicant respectfully traverses.

In particular, Applicant disagrees with the Examiner's assertion that the state of the art regarding JSRV is that there are no treatments or vaccines, and that the breadth of the claims is unreasonable. As disclosed above, the specification teaches that "Env protein(s) are particularly useful in sensitizing the immune system of an animal such that, as one result, an immune

response is produced which ameliorates the effect of an infection by a JSRV or related viral particle." Thus, when a subject is suffering from the effects of an infection by a JSRV, inducing an immune response would provide the therapeutic benefit of alleviating the symptoms associated with infection. Applicant respectfully asserts that ameliorating the effect of an infection is a form of treating the infection. Therefore, it is an object of the present invention to teach a novel method for treating the symptoms associated with JSRV infection.

Additionally, Applicant disagrees with the Examiner's assertion that there is no direction or guidance as to how to achieve a pharmaceutical benefit using a JSRV or JSRV polypeptide. "The fact that the specification is devoid of a working example is without significance. It is well established that examples are not necessary." (*Ex parte Nardi*, 229 USPQ 79 (PTO Bd Pat. App. & Intrf. 1986. As mentioned above, Applicant has amended claim 37 to include the limitation "wherein the immune response ameliorates the effect of an infection by a JSRV or related viral particle." Support for the amendment is found at page 62, lines 25-31, on which there is presented a therapeutic benefit to inducing an immune response to JSRV in a subject. Applicant therefore respectfully submits that amended claim 37 provides adequate guidance to achieve a pharmaceutical benefit using a JSRV or JSRV polypeptide.

Finally, Applicant disagrees with the Examiners assertion that it would require undue experimentation to make or use the invention. In *In re Brana*, the Federal Circuit held that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans" (*In re Brana*, 51 F.3d 1560, 1568 (Fed.Cir.1995). Whether undue experimentation is required is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. The factors to be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Some trial and error is

permissible. *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). As stated above, the specification provides adequate guidance to achieve a pharmaceutical benefit using a JSRV or JSRV polypeptide. It is therefore submitted that one of skill in the art would understand how to make and use the methods of the invention to induce an immune response using JSRV or JSRV polypeptide to ameliorate the effect of infection. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Applicant respectfully traverses the rejection of claim 3 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, claim 3 is drawn to a retrovirus having a genomic sequence as set forth in GenBank accession no. AF105220. The Examiner alleges that it is not clear what sequence is being referenced because the specification fails to disclose what sequence is contained in the deposit. Applicant respectfully submits that claim 3 has been cancelled, and thus the rejection is moot with regard to claim 3.

However, Applicant has amended the specification to include a sequence identification number for GenBank Accession no. AF105220, and has included the sequence in the Sequence Listing attached hereto. Further, Applicant has amended claim 1 to include the limitation of claim 3, and thus the above discussion is applicable to amended claim 1. Consequently, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejection Under 35 U.S.C. § 102

Applicant respectfully traverses the rejection of claims 1-3 under 35 U.S.C. § 102(b) as allegedly being anticipated by York et al (*Journal of Virology*, September 1991, 65:5061-5067; hereinafter "York"). Applicant has cancelled claim 3, thus rendering the rejection moot with

regard to claim 3. Regarding claims 1 and 2, Applicant's claims to an isolated replication competent infectious Jaagsiekte sheep retrovirus (JSRV) having a genomic sequence as set forth in SEQ ID NO:8 distinguishes over the disclosure of York, by requiring a JSRV GAG protein; a JSRV POL protein; a JSRV ENV protein; a JSRV genome comprising Long-Terminal Repeat (LTR) sequences at the 5' and 3' end of the retroviral genome, wherein the LTR is active in pulmonary epithelial cells, a polynucleotide sequence encoding JSRV GAG protein, JSRV POL protein, and JSRV ENV protein; and cis-acting nucleic acid sequences necessary for reverse transcription, packaging and integration in a target cell.

Applicant disagrees with the Examiner's assertion that York discloses all of the elements of Applicant's invention. More particularly, York does not disclose a JSRV having a genomic sequence as set forth in SEQ ID NO:8. York discloses "the deduction of a nucleotide sequence of a South African strain of JSRV (JSRV-SA)." (specification, page 2, lines 18-19). The JSRV provirus of the present invention ($JSRV_{21}$) "is 7 bp shorter than JSRV-SA and in particular has a 5-bp deletion in U3 with respect to JSRV-SA." (specification, page 61, lines 23-24). Further, "a reconstructed JSRV-SA provirus failed to reproduce SPA in sheep." (specification, page 2, lines 26-27). Example 1 demonstrates that animals inoculated intratracheally with concentrated $JSRV_{21}$ developed signs and symptoms of SPA. (specification, page 66, lines 9-34).

It is also noteworthy to mention that York fails to disclose or suggest LTRs and nucleic acid sequences encoding proteins for other functions, as indicated by the Examiner. In fact, the York reference does not contain page 4930 (see citation on page 7 of the Office Action). In addition, the Examiner relies upon Applicant's own work (Palmarini et al., *J. Virology*, 2000, 74:5776-5787; hereinafter "Palmarini") to prove that the activity of the LTR in pulmonary epithelial cells is an inherent property. However, Applicant respectfully draws the Examiner's attention to the priority date of the instant application (July 8, 1999), which precedes the date of publication of Palmarini (2000). Therefore, Applicant submits that Palmarini is not available as supporting evidence for a rejection under 35 U.S.C. § 102(b).

Since York fails to disclose each and every element of the invention, as defined by amended claim 1, Applicant respectfully submits that the disclosure of York does not establish anticipation of claims 1 and 2 under 35 U.S.C. § 102(b).

Rejection Under 35 U.S.C. § 103

Applicant respectfully traverses the rejection of claims 37-41 under 35 U.S.C. § 103(a) as allegedly being unpatentable over York as applied to claims 1-3 above, and further in view of Salk et al. (US Pat. No. 6,017,543; hereinafter "Salk") and Gilbert et al. (US Pat. No. 5,017,543; hereinafter "Gilbert").

The burden of proof in establishing a *prima facie* case of obviousness under § 103 clearly rests with the Patent Office. *In re Piasecki,* 745 F.2d 1468, 1472 (Fed. Cir. 1984). In establishing a *prima facie* case, the Patent Office, among other things, must show that (1) the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention; and (2) that the prior art would have revealed a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure." *Id.* Thus, "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000). Further, when relying on the knowledge of persons of ordinary skill in the art, the Patent Office must "explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). "The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with." *In re Sang Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) (citations omitted).

To date, the Patent Office has failed to provide objective evidence of any suggestion or motivation in the prior art to combine and modify the particular references cited by the Office. Instead, the Office has simply recited elements gleaned from the various references and stated that the combination of these elements would have been obvious to one skilled in the art. It is well settled that the Patent and Trademark Office cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention. *SmithKline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 887 (Fed. Cir. 1988). In addition, it is now well established that "[b]road conclusory statements regarding the teaching of multiple references standing alone are not 'evidence'." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999); see also *In re Kotzab*, 217 F.3d at 1370. "Th[e] factual question of motivation is material to patentability, and [can] not be resolved on subjective belief and unknown authority." *In re Sang Su Lee* 277 F.3d at 1343-44. Without such objective evidence to combine the references, it is inferred that the references were selected with the assistance of hindsight. *In re Rouffet*, 149 F.3d at 1358. It is well-established that the use of hindsight in the selection of references that comprise a case of obviousness is forbidden. *Id.*

The remarks above distinguishing the invention over the disclosure of York apply equally here. York neither teaches nor suggests a JSRV having a genomic sequence as set forth in SEQ ID NO:8 comprising Long-Terminal Repeat (LTR) sequences at the 5' and 3' end of the retroviral genome, wherein the LTR is active in pulmonary epithelial cells. Further, York fails to disclose inducing an immune response to JSRV in a subject comprising an immunogenically effective amount of a JSRV or JSRV polypeptide in a pharmaceutically acceptable carrier, wherein the immune response ameliorates the effect of an infection by a JSRV or related viral particle. Applicant respectfully submits that neither Salk nor Gilbert, or the combined disclosures thereof, cures the deficiencies of York for disclosing or suggesting the present invention.

Salk allegedly discloses retroviral immunogens to booster the immune response from a previous immunization. The retroviral immunogens are prepared from whole heat-inactivated virus. However, Salk does not disclose induction of an immune response to ameliorate the effect

of an infection by a JSRV. Salk states at col. 7, lines 32-39, "because the persistence or decline of immunoprotective factors anti-p24 and RTI...determine whether or not AIDS develops, it is now possible, using an appropriately formulated immunogen in serologically positive individuals, to stimulate an anamnestic response early enough to enhance and prolong, perhaps indefinitely, the continued presence of any immunoprotective factors induced by the initial response to infection." Applicant submits that there is no obvious indication in the art that use of heterologous genes in a viral vector will be successful. Consequently, because Salk is silent regarding the applicability of the methods to ameliorating the effects of JSRV, Salk is limited to the teachings of the disclosure related to HIV. Further, there is no suggestion, and thus, no expectation of successfully combining with the disclosure of York to arrive at Applicant's invention. Therefore, Applicant respectfully requests that the rejection be withdrawn.

The disclosure of Gilbert does not cure the deficiency of either York or Salk to suggest the present invention. Gilbert allegedly discloses immunogentic compositions comprising peptides from the envelope region of the HIV and adjuvants. The peptides of Gilbert "may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in immunologically effective amounts to protect patients for some time against HIV infection." Gilbert discloses peptides from specific regions of HIV to protect a subject from infection. As stated above, Applicant submits that there is no obvious indication in the art that use of heterologous genes in a viral vector will be successful. Consequently, because York, Salk and Gilbert are all silent regarding the applicability of their methods to ameliorating the effects of JSRV, all are limited to the teachings of the respective disclosures. Further, there is no suggestion in Gilbert, and thus, no expectation of successfully combining with the disclosures of York and Salk to arrive at Applicant's invention. Therefore, Applicant respectfully requests that the rejection be withdrawn.

Claims 4-12 are also rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kasahara et al (U.S. Pat. No. 6,410,313; hereinafter "Kasahara") in view of York. Kasahara discloses a recombinant replication competent retrovirus comprising gag, pol, env, and

oncoretroviral polynucleotide sequence comprising LTR sequences at the 5' and 3' end of the oncoviral genome, a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence and cis-acting nucleic acid sequences necessary for reverse transcription, packaging and integration in a target cell. However, Kasahara is silent on JSRV. The Examiner alleges that one would have had a reasonable expectation of success that York's virus would have worked in Kasahara's retrovirus design because JSRV is a retrovirus/oncovirus and shares the same properties as taught by Kasahara's retrovirus.

As mentioned above, Applicant submits that there is no obvious indication in the art that use of heterologous genes in a viral vector will be successful for stimulating an immune response and ameliorating the effect of an infection by a virus. Success with one retrovirus does not guarantee success with another. Consequently, because Kasahara is silent regarding the applicability of the methods to ameliorating the effects of JSRV, Kasahara is limited to the teachings of the disclosure. Further, there is no suggestion in Kasahara, and thus, no expectation of successfully combining with the disclosure of York to arrive at Applicant's invention. Therefore, Applicant respectfully requests that the rejection be withdrawn.

Accordingly, it is respectfully submitted that the Examiner has not met the burden of proving *prima facie* obviousness under 35 U.S.C. § 103(a), and withdrawal of the rejections is respectfully requested.

CONCLUSION

If the Examiner would like to discuss any of the issues raised in the Response, Applicants' representative can be reached at (858) 677-1456. The Commissioner is hereby authorized to charge any other fees that may be associated with this communication, or credit any overpayment to Deposit Account No. 50-1355.

Respectfully submitted,

Date: May 24, 2004

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Jaagsiekte Sheep Retrovirus and Lung Cancer

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CHAPTER 3

Natural History of JSRV in Sheep

J.M. SHARP, J.C. DEMARTINI

Abstract Ovine pulmonary adenocarcinoma (OPA) is a contagious lung tumour of sheep and, rarely, goats that arises from two types of secretory epithelial cell that retain their luxury function of surfactant synthesis and secretion. It is classified as a low-grade adenocarcinoma and is viewed as a good model for epithelial neoplasia because of its morphological resemblance to the human lung tumour, bronchioloalveolar adenocarcinoma.

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action with viral protein components, such as the envelope protein, an insertional mutagenesis event that specifically transforms these cell types, or transcriptional specificity of JSRV expression.

9

Immune and Inflammatory Responses to JSRV in OPA-Affected and Unaffected Sheep

An unusual, perhaps unique, feature of OPA is the absence of a specific humoral immune response to JSRV, despite the highly productive infection in the lungs and the disseminated lymphoid infection. Several studies have failed to detect antibodies to JSRV in sera or lung fluid of affected sheep by Western blotting or ELISA (SHARP and HERRING 1983; ORTIN et al. 1998; DEMARTINI et al. 1988; VERWOERD 1990; SUMMERS et al. 2002). The reactivity to recombinant JSRV CA in sera from affected sheep, described in some accounts (KWANG et al. 1995), was shown not to be specific and reflected the presence of antibodies to the GST fusion partner of the recombinant antigen used in the assays (ORTIN et al. 1998). However, antibodies can be detected readily in the serum and lung lavage of sheep immunized with recombinant JSRV CA or SU in adjuvant (J.M. Sharp, P. Dewar and R. van der Molen, unpublished results). These results indicate that sheep are not inherently unresponsive to JSRV antigens and that the apparent tolerance, perhaps as a consequence of endogenous sequences expressed in utero (PALMARINI et al. 2001) or as a direct consequence of infection by JSRV, can be broken. To date, specific cellular immune responses have not been investigated. Another prominent feature of naturally OPA-affected sheep is the marked peripheral neutrophilia and lymphopaenia, particularly affecting $CD4^+$ T lymphocytes although other subsets remained unaffected (ROSADIO and SHARP 1992; HOLLAND et al. 1999; SUMMERS et al. 2002).

The persistent and disseminated infection of the lymphoreticular system by JSRV and dysregulation of the immune and inflammatory responses of infected sheep suggest that JSRV may interfere with the host immune responses. This notion is supported by studies demonstrating JSRV infection of a wide range of lymphoid cells (HOLLAND et al. 1999). These workers showed that in naturally infected sheep, JSRV proviral burden was greatest in the macrophage/monocytic cell population (1/2500 cells), followed by B cells (1/3800 cells), $CD4^+$ T lymphocytes (1/6800 cells) and $CD8^+$ T lymphocytes (1/16700 cells). Furthermore, dissemination of